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Outcome of Patients With a History of Bilateral Retinoblastoma Treated for a Second Malignancy: The Memorial Sloan-Kettering Experience

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Background. Patients with bilateral retinoblastoma are well recognized to have a high risk of developing a second malignancy, but there are little published data regarding the outcome of these patients following treatment.

Patients and Methods. We identified 15 patients with a history of bilateral retinoblastoma who received treatment at Memorial Sloan-Kettering Cancer Center for a newly diagnosed second malignancy. The median age of second tumor occurrence was 18 years (range 10–32 years). Three patients later had a third tumor (18 tumors total). Tumor sites included facial structures in 14 cases and extremities in 4. Histologies included osteosarcoma (5), leiomyosarcoma (5), high-grade spindle cell sarcoma (3), malignant fibrous histiocytoma (3), malignant mesenchymoma (1), and angiosarcoma (1).

Results. Nine patients are alive: 7 disease free at a median of 29 months (range 6–214 months) and 2 with residual disease 59 and 148 months post-diagnosis of the second malignancy. Six patients have died at a median of 31 months (range 16–98 months) after diagnosis of the second malignancy.

Conclusions. Patients with a history of bilateral retinoblastoma who develop a second malignancy may enjoy extended periods of survival. Aggressive therapy appropriate to the tumor histology and site is indicated. Med. Pediatr. Oncol. 30:59–62, 1998.

Key words: retinoblastoma; neoplasm, second primary; chemotherapy, adjuvant; radiation therapy; surgery

INTRODUCTION

Retinoblastoma (RB) is the most common primary ocular malignancy of childhood [1,2]. It is well recognized to occur in two patterns: a non-genetic form presenting with unilateral disease and a genetic form. The genetic form is associated with a germline defect in the RB1 gene and usually presents with bilateral disease, though approximately 10% of patients with unilateral disease also have the germline defect. Patients with bilateral RB have an approximately 90% chance of a cure of their primary disease, but have been found to have a greatly elevated risk of developing a second malignancy in comparison with the cancer risk of the general population [3–5]. Radiation therapy used to treat the RB shortens the latency period, but second malignancies also occur outside of the portals and in patients with bilateral RB who have never been irradiated [6].

In spite of this being a well-recognized problem, there are very little published data addressing the treatment and outcome of patients with a history of bilateral RB once they are diagnosed with a second malignancy. In the most detailed report, Smith et al. [7] described their results treating 8 such patients and recommended an aggressive approach. Combined modality therapy with surgery, radiation therapy, and chemotherapy produced 22–72+ months of disease-free survival in 4 of 5 patients vs. no survivors in 3 patients treated less aggressively [7]. In this report, we describe the therapy and outcome of 15 patients with a history of bilateral RB treated for a second malignancy at Memorial Sloan-Kettering Cancer Center.

PATIENTS AND METHODS

We reviewed our institutional experience treating patients with a history of bilateral RB who presented with a second malignancy. Ascertainment of cases was accomplished via a survey of the attending staff at Memorial Hospital, search of the hospital data base, and by review of the records of the Ophthalmic Oncology Center at New York Hospital. Thorough chart reviews of the

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TABLE I. Clinical Summary of Patients With Second Malignancies*

Patient	RB treatment		Age (years)	Site	Pathology	Surgery	RT	Chemotherapy (initial regimen)	Survival (months)
	Left eye	Right eye							
1	E, RT	RT	12	Right ethmoid	Leiomyosarcoma	Resection	Yes		24+
			14	Upper lip	Angiosarcoma	Resection	No		
2	E	RT	13	Right femur	Osteosarcoma	Resection	No	HDMTX, BCD, V	148+
			23	Left sphenoid	Leiomyosarcoma	Resection	Yes		
3	RT	E	26	Left orbit	MFH	Resection	No	HDMTX, BCD, A	98
4	RT	E	19	Left orbit	HGS	Resection	No	HDMTX	59+
5	RT	E, RT	16	Left tibia	Osteosarcoma	Resection	No	HDMTX, BCD, C, A	35
			18	Right orbit	MFH	Resection	No	HDMTX	
6		RT	32	Right ethmoid	Leiomyosarcoma	Resection	Yes		6+
7	E	RT	11	Right orbit	MFH	Resection	PD	HDMTX	73
8	RT	E	20	Left femur	HGS	Resection	No	HDMTX, I, C, A	25+
9	E	E, RT	10	Right maxillary sinus	Leiomyosarcoma	Biopsy	PD	HDMTX, C, A	16
10	RT	E	19	Left ethmoid	Osteosarcoma	Resection	No	HDMTX, BCD, A	91+
11	E, RT	E	18	Left maxillary sinus	Leiomyosarcoma	Resection	Yes		29+
12	RT	E	14	Left orbit	Osteosarcoma	Biopsy	No	HDMTX, BCD, V, I, A	27
13	E, RT	E	22	Left thigh	Mesenchymoma	Resection	Yes		24
14	E, RT	E, RT	13	Left maxilla	Osteosarcoma	Resection	No	HDMTX, BCD, A	214+
15	E, RT	RT	18	Left malar	HGS	Resection	No	HDMTX	102+

*E = enucleation; RT = radiation therapy; MFH = malignant fibrous histiocytoma; HGS = high-grade sarcoma; PD = at time of progressive disease; HDMTX = high-dose methotrexate; BCD = bleomycin, cyclophosphamide, dactinomycin; I = ifosfamide; C = cisplatin; A = doxorubicin; V = vincristine; + = still alive.

cases identified were performed. Only patients who received therapy at Memorial Hospital for a newly diagnosed second malignancy were included; those who were referred to this institution with recurrent or refractory disease were excluded from this analysis. Survival was defined as the interval between diagnosis of the second malignancy (the first second malignancy in patients who later developed a third tumor) until death, or until the time of the last documented follow-up for the patients who are still alive. Information is current as of the last patient contact to March 1, 1996. Pathological specimens from each patient were reviewed by one of the authors (W.L.G.) and all of the radiologic studies available were reviewed by another (N.S.R.).

RESULTS

Table I summarizes the 15 patients with a history of RB who were treated for a second malignancy at our center since 1978. Thirteen of them were originally treated for their RB by the ophthalmologists at the Ophthalmic Oncology Center at New York Hospital (or at Columbia Presbyterian where the Center was formerly located). In the same time period, about 70 patients from that center developed second malignancies. Generally these patients were offered referral to the Memorial Sloan-Kettering Cancer Center; however, because of geographic issues or personal preference, only the subset of patients discussed in this report actually received their initial care at Memorial.

Fourteen patients had a history of bilateral RB. One patient (patient 6) had multifocal unilateral disease with a positive family history, indicative of a germline RB1 mutation, and therefore he was included in the analysis. The median age of second malignancy occurrence was 18 years (range 10–32 years). Three patients later developed third malignancies. Cases defined as third malignancies were clearly distinct from the second malignancy due to different tumor histopathology. The sites included facial structures in irradiated areas in 13 cases, extremities in 4, and face (but apparently outside of the irradiated field) in 1. Metastatic disease was not detected at the time of diagnosis of the second malignancy in any case. Histologies included 5 cases of osteosarcoma, 5 leiomyosarcoma, 3 high-grade spindle cell sarcoma, 3 malignant fibrous histiocytoma (MFH), 1 malignant mesenchymoma, and 1 angiosarcoma. Review of the pathology confirmed the diagnoses.

These patients were not enrolled on a single protocol, but they were treated in a fairly uniform manner in this single institution. The patients with osteosarcoma, MFH, or high-grade sarcoma generally had an initial diagnostic biopsy, received neoadjuvant high-dose methotrexate (HDMTX)-based chemotherapy prior to definitive surgery, and postoperatively continued with additional chemotherapy. Radiation therapy was not administered as part of the initial treatment regimen, but instead was reserved for time of failure. After neoadjuvant chemotherapy 6 of the 8 facial tumors with these histologies were completely resected. Two that were not resected

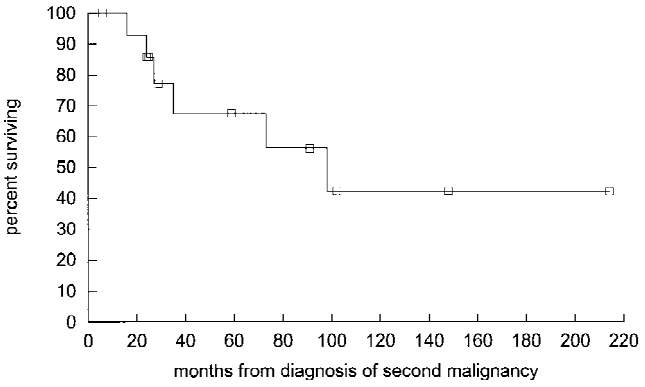

Fig. 1. Survival from time of diagnosis of the second malignancy.

had significant improvements documented by magnetic resonance imaging (MRI) (63% and 64% shrinkage, respectively).

Four of the 5 patients with leiomyosarcomas were treated with resection and adjuvant radiation therapy. The other was treated with neoadjuvant chemotherapy after a diagnostic biopsy and her tumor proved to be refractory to all chemotherapy (HDMTX, cisplatin/doxorubicin, ifosfamide/etoposide, 5-fluorouracil/leucovorin, and thiotepa) administered. An additional patient (patient 13) had her initial biopsy interpreted as a leiomyosarcoma and proceeded to a resection without neoadjuvant chemotherapy. At resection the tumor was noted to have elements of both osteosarcoma and leiomyosarcoma and was reclassified as a malignant mesenchymoma.

Nine patients are alive. Seven are disease free at a median of 29 months post-diagnosis of the second malignancy (range 6–214 months). Two others are alive, but with residual disease, at 59 and 148 months. Six patients have died after surviving a median of 31 months from diagnosis of the second malignancy (range 16–98 months). The median time of survival from diagnosis of the second malignancy is 35 months (range 6–214 months). A Kaplan-Meier plot of survival is shown in Figure 1, but it should be noted that the limited number of patients makes the confidence intervals wide.

DISCUSSION

Children diagnosed with RB have an excellent chance of surviving their primary disease with therapy utilizing surgery and radiation therapy [8,9]. Unfortunately, those patients with the germline defect of the RB1 gene—all bilateral patients and approximately 10% with unilateral disease—have a significant risk of developing a second malignancy. Eng et al. [10] reported that 919 patients with a history of bilateral RB had a 26% risk of mortality from a second malignancy by 40 years after their original diagnosis. Other authors, reporting on smaller numbers of patients, have reached similar conclusions.

Despite the extensive documentation of this problem, very little has been published in the medical literature regarding the treatment and outcome of these patients once they have developed their second malignancy. Smith et al. [7,11] reported their experience treating 8 children with a history of bilateral RB who developed second malignancies and then reviewed the limited literature. Their patients developed 11 secondary tumors, with 3 patients having third tumors. Eight of the tumors developed in the irradiated field. Histologies included 7 cases of osteosarcoma, 1 angiosarcoma, 1 rhabdomyosarcoma, 1 MFH, and 1 unclassified round blue cell tumor. No patient presented with distant metastases. Retrospectively, they divided the patients into two groups. Five patients had been treated aggressively with radical resection and postoperative radiation therapy and/or chemotherapy. Four of these patients were disease-free survivors at 22–72 months. Three patients were felt to have been managed less aggressively and all died.

Cole et al. [12] included 2 patients with a history of RB in their report on MFH in children. One was inoperable, failed to respond to HDMTX and died, while the other had a ''subtotal enucleation'' and remained with no evidence of disease at 26 months despite no further therapy. Pillay et al. [13] included 1 child with a history of bilateral RB in their report of ''successful treatment'' of osteosarcoma as a second malignancy. He received radiation therapy and HDMTX, vincristine, cisplatin, and doxorubicin, had a complete radiographic response, but relapsed at 18 months and subsequently died.

Investigators at M.D. Anderson reviewed the outcome of patients with second malignancies after treatment of childhood cancer, though therapy for the second malignancies was not described [14]. Twenty patients with a history of RB developed a second malignancy, 10 of which were osteosarcoma. Six of these were in the irradiated field (periorbital), were felt to be unresectable, and proved fatal. Four were extremity lesions and 2 of these patients were free of disease, though no mention of time of follow-up was made.

Most recently, investigators from the St. Jude Children's Research Hospital described six survivors of bilateral RB who developed second malignancies [15]. Histologies included 4 cases of osteosarcoma, 1 basal cell carcinoma, and 1 Ewing's sarcoma. Only the Ewing's sarcoma was outside of the irradiated field. Of the 4 patients with osteosarcoma, 3 did not receive any chemotherapy and died of their disease. One received chemotherapy (unspecified) along with surgery and was reported to be disease free. The patient with a basal cell carcinoma was disease free after resection only, and the

patient with Ewing's sarcoma died despite treatment with chemotherapy.

CONCLUSIONS

Our data, in conjunction with the data of Smith et al. [7], suggest that an aggressive approach with curative aim is indicated in patients with a history of bilateral RB who develop a second malignancy. Our patients with osteosarcoma, MFH, or high-grade sarcoma were treated with HDMTX-based chemotherapy regimens and aggressive surgery, and those with leiomyosarcoma were treated with aggressive surgery and radiation therapy, but this is not necessarily optimal for future patients. We would advocate treatment according to the contemporary state of the art for the tumor histology and site, and with recognition of any limitations imposed by prior treatment of the RB. This approach can provide extended periods of survival for most of these patients.

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REFERENCES

1. Donaldson SS, Egbert PR, Lee W: Retinoblastoma. In Pizzo PA, Poplack DG (eds): ''Principles and Practice of Pediatric Oncology.'' Philadelphia: Lippincott, 1993, pp. 683–696.
2. Abramson DH: Retinoblastoma 1990: Diagnosis, treatment, and implications. Pediatr Ann 19:387–395, 1990.
3. Hawkins MM, Draper GJ, Kingston JE: Incidence of second primary tumours among childhood cancer survivors. Br J Cancer 56:339–347, 1987.
4. Kingston JE, Hawkins MM, Draper GJ, Marsden HB, Kinnier-Wilson LM: Patterns of multiple primary tumours in patients treated for cancer during childhood. Br J Cancer 56:331–338, 1987.
5. Tucker MA, D'Angio GJ, Boice JD Jr, Strong LC, Li FP, Stovall M, Stone BJ, Green DM, Lombardi F, Newton W, Hoover RN, Fraumeni JF: Bone sarcomas linked to radiotherapy and chemotherapy in children. N Engl J Med 317:588–593, 1987.
6. Newton WA, Meadows AT, Shimada H, Bunin GR, Vawter GF: Bone sarcomas as second malignant neoplasms following childhood cancer. Cancer 67:193–201, 1991.
7. Smith LM, Donaldson SS, Egbert PR, Link MP, Bagshaw MA: Aggressive management of second primary tumors in survivors of hereditary retinoblastoma. Int J Radiat Oncol Biol Phys 17:499–505, 1989.
8. Shields JA, Shields CL: ''Intraocular Tumors: A Text and Atlas.'' Philadelphia: W.B. Saunders, 1992.
9. Abramson DH: Treatment of retinoblastoma. In Blodi FC (ed): ''Retinoblastoma.'' New York: Churchill Livingstone, 1985, pp. 3–93.
10. Eng C, Li FP, Abramson DH, Ellsworth RM, Wong FL, Goldman MB, Seddon J, Tarbell N, Boice JD: Mortality from second tumors among long-term survivors of retinoblastoma. J Natl Cancer Inst 85:1121–1128, 1993.
11. Smith LM, Donaldson SS: Incidence and management of secondary malignancies in patients with retinoblastoma and Ewing's sarcoma. Oncology 5:135–141, 1991.
12. Cole CH, Magee JF, Gianoulis M, Rogers PCJ: Malignant fibrous histiocytoma in childhood. Cancer 71:4077–4083, 1993.
13. Pillay R, Graham-Pole J, Novak L, Kurczynski E, Yulish BS: Successful treatment of osteogenic sarcoma developing as a second cancer in childhood. Am J Pediatr Hematol Oncol 5:103–105, 1983.
14. Smith MB, Xue H, Strong L, Takahashi H, Jaffe N, Ried H, Zietz H, Andrassy RJ: Forty-year experience with second malignancies after treatment of childhood cancer: Analysis of outcome following the development of the second malignancy. J Pediatr Surg 28:1342–1349, 1993.
15. Fontanesi J, Parham DM, Pratt C, Meyer D: Second malignant neoplasms in children with retinoblastoma: The St. Jude Children's Research Hospital experience. Ophthalmic Genet 16:105–108, 1995.